REMARKS

Favorable reconsideration of the subject application, as amended above, is respectfully requested in view of the comments below.

Claims 1-3 and 6-28 are pending in the subject application. Claims 7 and 14-28 have been canceled. Accordingly, claims 1-3, 6 and 8-13 are presented for examination on the merits.

Claim 1 has been amended to recite that the insulin secretory signal is operably linked to a mature somatotropin. Support for this amendment is found in Figures 1 and 2, where it is demonstarated that the insulin secretory signal is fused to the mature somatatropin (190 amino acids) *via* a two amino acid linker (Leu-Glu). Claim 3 has been amended to correct a typographical error and delete the term"substantially."

Accordingly, no new matter is added by these amendments to the claims.

Applicants acknowledge the finality of the restriction requirement.

I. Objection to the Drawings

Applicants enclose herewith a replacement copy of the drawings (FIGS. 3-5 and 7-13).

II. Claim Objections

It is respectfully submitted that the amendment to claim 3 and cancellation of claim 7 render the formal grounds of rejection moot.

III. Rejection of Claim 1, 8-11 and 13 Under 35 U.S.C. § 103(a)

Claims 1, 8-11 and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentably obvious over Ernst et al., in view of Paulson et al., further in view of Eskridge et al.. The Examiner states that Ernst et al. teaches enhanced secretion of heterologous protein by the **addition of** a heterologous secretion signal to the protein. Paulson et al. is relied on as teaching fusion of a pre-insulin secretory signal to a gene encoding a protein not normally secreted. Eskridge et al. is relied on as teaching the sequence of the signal secretory signal required to obtain secretion of protein. The Examiner concludes, therefore, that one of ordinary skill in the art would have been motivated on the basis of the combined prior art to use the pre-insulin secretory signal in the expression vector of Ernst et al. to express somatotropin and for the expected benefit of secretion of the protein from the host cells.

Applicants respectfully disagree with the Examiner's conclusion.

The present invention is directed to expression vectors and expression cassettes that contain a sequence encoding an insulin secretory signal operably linked to a heterologous sequence encoding mature somatotropin. Thus, the vector and cassette of the present invention require the replacement of the native somatotropin secretory signal with an insulin secretory signal. Moreover, expression of the somatotropin fusion gene results in enhanced secretion of the protein.

In contrast, the combined prior art fails to teach or suggest replacement of a homogenous secretory signal with a heterogenous secretory signal, particulary the insulin pre-secretory signal to obtain enhanced secretion of a recombinant protein. The primary reference, Ernst et al., is directed to a means of achieving secretion of a recombinant

protein from a yeast cell. There is no mention of the use of the insulin secretory signal, and the preferred secretory signals are yeast sequences. Moreover, it is clear from the disclosure at column 6, lines 41-50 and column 8, lines 66 to column 9, line 1, that the heterologous secretory signal is linked to a precursor protein, i.e, a protein that includes the native secretory signal, and there is no disclosure or suggestion in this reference that the native secretory signal be replaced with another, heterologous secretory signal, as in the claimed invention. Further, the primary reference does not teach or suggest that secretion of a heterologous protein can be achieved in any cells other than yeast cells, and in particular, expression and secretion from mammalian cells is not disclosed or suggested.

Neither Paulson et al., or Eskridge eta l. cure the deficiencies of the primary reference. Paulson et al. discloses the expression and secretion of a sialyltransferase polypeptide from an insect cell line which involves expressing an enzymatic portion of a polypeptide lacking its transmembrane anchor domain with a heterologous secretory signal, specifically the pre-insulin secretory signal. There is no teaching or suggestion of using the expression/secretion system with somatotropin, nor is there any teaching or suggestion of replacing a native secretory signal with the insulin secretory signal, since the sialyltransferase polypeptide does not contain a secretory signal. Finally, there is no teaching or suggestion of the enhanced secretion of the heterologous protein observed with the present invention.

Eskridge et al., relates to a study to identify sequences in the "amino terminus of preproinsulin" that are necessary for mediating intracellular sorting and secretion of the bacterial enzyme, chloramphenical acetyltransferase (CAT). Contrary to the Examiner's

assertion, this document teaches away from the use of the insulin secretory signal alone, and instead, teaches the necessity of additional sequences with the insulin secretory signal sequences. The authors of the study were aware of the region of the amino terminus which constitutes the secretion signal, but they did not select to use the secretory sequence alone, indicating that they did not consider it to be sufficient to achieve secretion .(See paragraphs 1 and 3 of the introductory passages on pages 2263 and 2265) Eskridge et al tested sequences containing 38 amino acids and 71 amino acids which include the insulin secretory signal, but they did not test the secretory signal alone.

Moreover, these authors only teaches the use of the first 38 amino acids of preproinsulin for the secretion of CAT, which is a cytoplasmic enzyme and therefore, is not normally secreted. Thus, Eskridge accomplished little more thanPaulson et al., i.e., added a secretory signal to a protein normally lacking such a signal and achieving secretion. However, this reference, like the two references discussed above, fails to disclose or suggest that replacement of the naturally occurring secretory signal of a secreted protein with the insulin secretory protein results in enhanced secretion. As such, the combination of references fails to disclose or suggest the claimed invention.

Accordingly, the rejection of claims 1, 8-11 and 13 under 35 U.S.C. § 103(a) is respectfully traversed.

IV. Rejection of Claims 3 and 7 Under 35 U.S.C. § 112, Second Paragraph

It is respectfully submitted that the rejection of claims 3 and 7 is rendered moot by the amendments to the claims.

V. Rejection of Claim 7 Under 35 U.S.C. § 112, First Paragraph

It is respectfully submitted that the rejection of claim 7 is rendered moot by cancellation of the claim.

It is respectfully submitted that the application, as amended above is in condition for allowance, an early notification thereof being earnestly solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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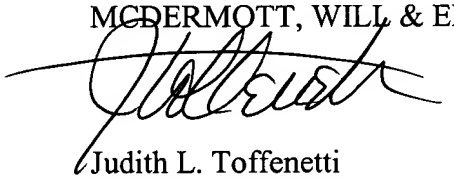

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